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JOURNAL ARTICLE

Compartmental Models with Spatial Diffusion: Estimation for Bone-Seeking Tracers

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ABSTRACT

A compartmentlike model is developed for tracers in which bone-volume diffusion plays an important role in body distribution (e.g. bone-volume-seeking metals). The model requires solution of an infinite eigensystem. Approximations are presented for cylindrical diffusion in canalicular territory. An application to lead metabolism in beagle dogs suggests that finite truncation of the system of equations provides an adequate approximation for routine use in computer programs for compartmental-parameter estimation. The model is consistent with both power-law and exponential mixture retention functions.

1. INTRODUCTION

It is often assumed that an organism can be described by a finite number n of discrete compartments or pools, and that the mass $X(i,t)$ of tracer in compartment i at time t can be described by a mixture of at most n exponential functions of t. The underlying assumption here is that the evolution of $X(i,t)$ is governed by a coupled system of n linear differential equations with constant fractional exchange coefficients $k(i,j)$ from compartment j to compartment i [1]. It is also known that many substances have either organ retention functions $X(i,t)$ (e.g. in blood), or whole-body retention functions $R(t) = \Sigma X(i,t)$ that can be described far more simply by a power function, or a sparse collection of exponential and power functions, of t. These include lead and many alkaline-earth metals [2–4], indicator dyes, and other substances [5, 6]. Many models have been proposed for these observations [7]. The models which we find most convincing are those based on diffusion of tracer through dense materials such as bone [8, 9] and liver acinus [10]. The solution of diffusion equations in a homogeneous medium with simple geometry is well known [11, 12]. However, the organ or organ system in which diffusion is occurring is connected to other organs in the

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body for which the usual compartmental formulation may be more appropriate. Thus the problem consists of finding the solution of a coupled system of linear first-order and second-order equations. We will here present a simple solution which is particularly useful for purposes of estimation of the kinetic parameters from such a system.

2. DIFFUSION IN A CYLINDER

For bone diffusion models it is convenient to assume cylindrical diffusion. The physiological basis for this is the assumption that ions of tracer are transported through the blood to the tiny vessels or canaliculi that permeate the bone volume, and are transported by diffusion from the canalicular surface at which they are deposited throughout the bone. Many of the ions deposited at the canalicular surface return to the same surface, but a substantial fraction of the ions may eventually escape the bone volume through some distant canaliculus. The canaliculi feed into a central blood vessel in the Haversian canal. At some distance from the Haversian canal is a cement line across which the canaliculi do not communicate. The Haversian canal together with the surrounding material up to the cement line is known as an osteon. Adult cortical bone interior to the lamellar bone is dominated by Haversian systems (Fig. 1).

Assume the entry canaliculus is a cylinder of the Haversian canal of radius a, and let r denote the radial distance from the center of this cylinder. Let b denote the radius that defines the limit of canalicular territory [8, 9]. This is, approximately, the averaged distance between adjacent canaliculi. Such a description is crude, but quite useful. In reality, one would need to regard the distance b as a random variable.

Let $Q(r,t)$ be the concentration of tracer ions at radius r at time t. The basic diffusion equation is thus

$$\frac{\partial Q(r,t)}{\partial t} = D\left\{\frac{\partial^2 Q(r,t)}{\partial r^2} + \frac{1}{r}\frac{\partial Q(r,t)}{\partial r}\right\}. \tag{1}$$

One of the most difficult problems in applying our method is the specification of the boundary conditions for loss of ions from the canalicular territory. The radius b serves only to scale the diffusion process, since a completely homogeneous diffusion into a completely homogeneous medium with regularly spaced canaliculi (e.g. on a square or triangular lattice) would have zero concentration gradient along the surface of a polygonal prism surrounding each canaliculus (Fig. 2). Because the loss of ions is not homogeneous, we will assume that there is a first-order concentration gradient at radius b,

$$\frac{\partial Q}{\partial r} = -\frac{cQ}{b} \qquad \text{at} \quad r = b, \tag{2}$$

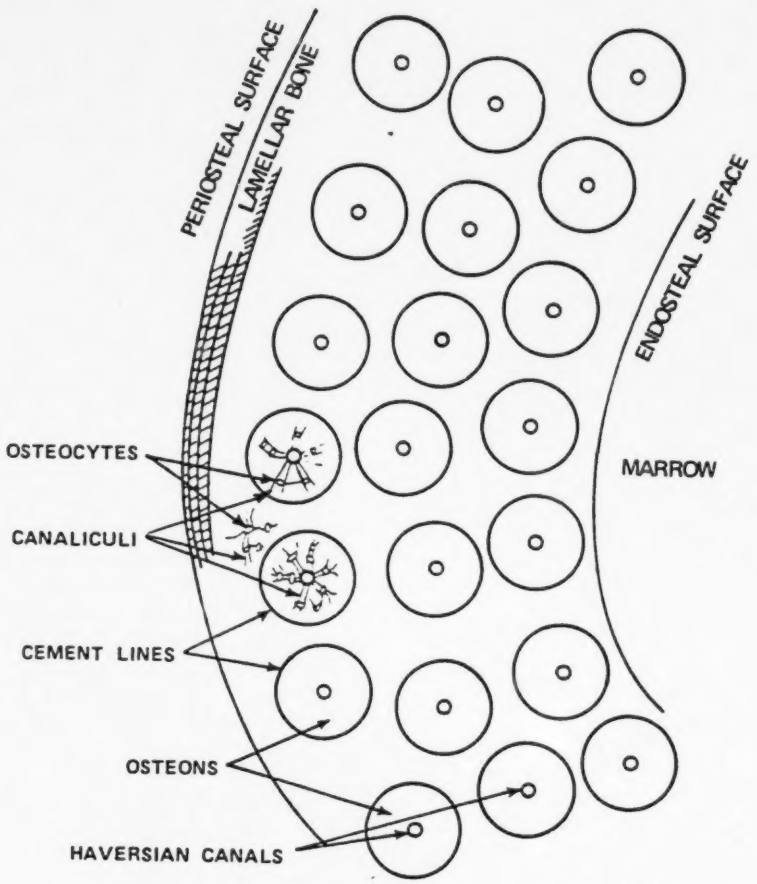

FIG. 1. Sketch of cross-sectional structure of bone, as simplified for use in this paper (see [14, p. 3]). Osteons are relatively smaller and far more numerous than suggested here.

where c is a dimensionless gradient-flow parameter that can be adjusted to fit the data.

The canalicular territory is assumed to be a hollow cylinder of inner radius a. If a is very small (as is assumed to be the case), then in many applications it will be convenient to set $a = 0$ and not specify a spatial boundary condition for the canaliculus. The fractional density of ions deposited at depth r in the canalicular territory from an initial bolus in the canaliculus is denoted $f(r)$, where L is the length of the cylinder and

$$\int_a^b 2\pi r L f(r)\, dr = 1. \tag{3}$$

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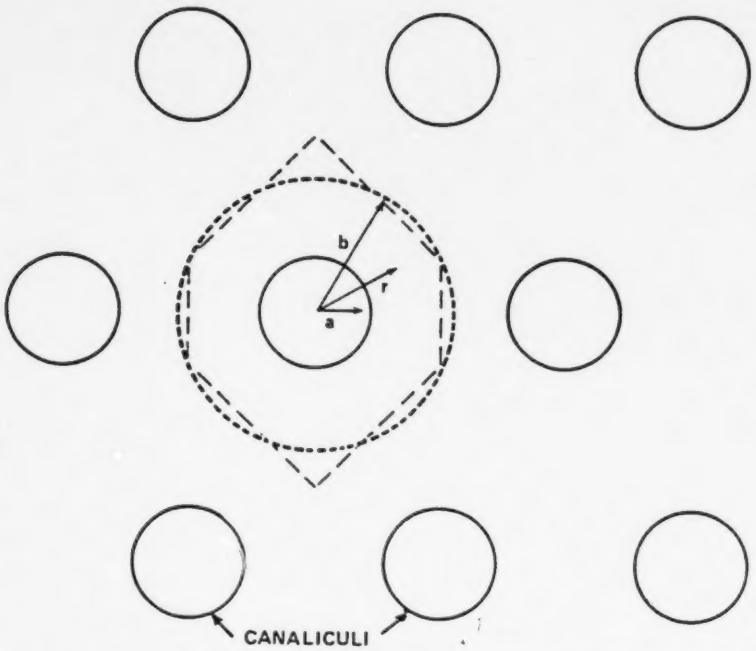

FIG. 2. Sketch of cross-section across circular canaliculi. The canalicular territory is shown as a hexagonal prism here, with its approximation by a circular cylinder.

By standard separation-of-variable techniques, the general solution for finite b can be shown to be an infinite series.

$$Q(r,t) = \sum_{j=1}^{\infty} \alpha(j) \exp\left(- \frac{D\theta(j)^2 t}{b^2} \right) U(r, \theta(j)). \tag{4}$$

The constants $\alpha(j)$ depend on the initial condition and may be adjusted to the data. The spatial part of the diffusion equation has eigenfunctions $U(r,\theta)$ and eigenvalues θ. The eigenvalues $\theta(j)$ for the spatial part of the diffusion equation depend on the boundary conditions. These are treated in very complete detail by Carslaw and Jaeger [11, p. 332]. Let $J_n(\theta)$ and $Y_n(\theta)$ be Bessel functions of order n of the first and second kinds respectively. When $a = 0$, Equation (2) implies that the $\theta(j)$ are positive roots of

$$\theta J_1(\theta) - cJ_0(\theta) = 0. \tag{5}$$

These eigenvalues have been extensively tabulated [11, 13]. When $a > 0$, Equation (2) and $Q(a,t) = \text{const}$ implies

$$\theta\{Y_0(a\theta/b)J_1(\theta) - J_0(\theta a/b)Y_1(\theta)\} + C\{J_0(a\theta/b)Y_0(\theta) - J_0(\theta)Y_0(a\theta/b)\} = 0 \qquad (6)$$

These eigenvalues have not been tabulated. We will use only (2) and (5) in the remainder of this paper.

For Equations (2) and (5), appropriate when $a = 0$, the orthogonal eigenfunctions U are proportional to $J_0(r\theta(j)/b)$.

Some analytical solutions are feasible, if $f(r)$ is not too complicated; e.g. [11, p. 202] if $f(r) = 1/\pi b^2 L$,

$$Q(r,t) = \sum_{j=1}^{\infty} \exp\left(-\frac{D\theta(j)^2 t}{b^2}\right) J_0\left(\frac{\theta(j)r}{b}\right) \frac{2c}{\left[J_0(\theta(j))^2 + c^2\right]\pi b^2 L},$$

where c is dimensionless.

If there is a unit instantaneous bolus at $r = R$, then [11, p. 369]

$$Q(r,t) = \sum_{j=1}^{\infty} \exp\left(-\frac{D\theta(j)^2 t}{b^2}\right) \frac{J_0(\theta(j)r/b)J_0(\theta(j)R/b)}{\pi b^2 L\left[J_0(\theta(j))^2 + J_1(\theta(j))^2\right]} \qquad (7)$$

The superposition of solutions (7) can generate arbitrary initial conditions because of the linearity of the diffusion equation.

3. COMPARTMENTAL MODELS WITH BONE DIFFUSION FROM A THIN CANALICULUS

We now assume that there are $n-1$ compartments for which linear kinetics apply (including possibly the bone surfaces); based on the foregoing discussion, we will approximate the entire bone volume by a system of cylindrical canalicular territories of radius b and total length L in which canaliculi of radius a are centered. The mass of tracer material in compartment i is $X(i,t)$. Compartment n is the total bone canalicular territory, and $Q(r,t)$ denotes the concentration of substance at radius r in the canalicular territory. We assume that the tracer may enter the canalicular territory at some radius r between a (the canalicular surface) and $b > a$, where $f(r)$ is the density at initial deposition. Let $A(i,t)$ denote the mass of tracer absorbed directly from the outside environment into compartment i.

Certain approximations will now be made based on the physical dimensions of the osteon and canalicular territory. Haversian canals are close together in compact cortical bone, on the order of 0.022 cm [14] and closer.

We may thus take the radius of an osteon as about 0.01 cm. The Haversian canal is much smaller than the osteon. A typical value for the Haversian-canal radius would be about 10 μm = 0.001 cm. The canalicular territory and its central canaliculus [8, 9] have radii of 0.075 μm = 7.5×10^{-6} cm and 0.85 μm = 8.5×10^{-5} cm. Thus the typical time scale for an ion traversing these radii by diffusion, r^2/D, is:

Osteon:	31,700 years
Haversian canal:	317 years
Canalicular territory:	2.29 years
Canaliculus:	6.51 days

We have assumed $D = 10^{-16}$ cm^2/sec [8, 9]. It is thus clear that for ion loss on time scales of a few weeks to many years, it would be reasonable to assume that: (i) most ions returning to the blood do so through the same canaliculus by which they were initially deposited; (ii) ions returning by diffusion after some years may well do so through other canaliculi or the Haversian canal; (iii) there is little loss of accuracy in modeling long-term kinetics of diffusion by assuming a thin canaliculus ($a = 0$), since the diffusion transit time across the canaliculus is so short (about 1 week). We thus adopt the following formulation.

TRACER TRANSPORT IN BLOOD AND TISSUE

Let $k(i,m)$ be the fractional transport coefficient from compartment on into i, where $i = 0,1,\ldots,n-1$, and $m = 1,\ldots,n-1$. Assume the canaliculi are of total length L and radius a which is very small but positive, so that the amount of tracer per unit time returned from bone (compartment n) to compartment i is $k(i,n)\pi a^2 LQ(0,t)$, where $Q(0,t)$ is the concentration at the canaliculus. Then

$$\frac{dX(i,t)}{dt} = \sum_{m=1}^{n-1} k(i,m)X(m,t) + k(i,n)\pi a^2 LQ(0,t) + A(i,t). \quad (8)$$

The fractional transfer coefficients satisfy

$$k(i,j) \geq 0 \qquad \text{for} \quad i \neq j,$$

$$k(i,i) = -\sum_{j=1, j\neq i}^{n} k(j,i) - k(0,i).$$

TRACER TRANSPORT INSIDE CANALICULAR TERRITORY

Equations (1) and (2) define cylindrical diffusion between the canaliculus and the limit b of canalicular territory. For purposes of modeling we take the

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inner radius of the territory as 0. The diffusion component is coupled to ion exchange between bone and blood in the canaliculus (see below) so that the left-hand side of (1) is only that component of $\partial Q/\partial t$ attributable to diffusion.

We should also like to represent aggregate loss of tracer ions due to escape through the distant canaliculi, the Haversian canal, etc. In view of the randomly nonhomogeneous geometry of the canaliculi in an osteon, I do not know how to model this. It may be reasonable to set the distances $r(j) > b$ of the more distant canaliculi and to reduce $\partial Q(r,t)/\partial t$ by

$$E(t) = \sum_{j=1}^{\infty} g(j)Q(r(j),t),$$

where the constants $g(j)$ can be adjusted to fit the geometry and the data. For a first approximation, I have set $E(t) = 0$. The tracer ions are returned to blood and tissue by the canaliculi, so this effect is measured in (8) by $k(i,n)$.

TRACER EXCHANGE AT THE CANALICULUS

Tracer ions enter the canaliculi from compartment m at a rate proportional to the mass $X(m,t)$ in that compartment. Assuming that all canaliculi are equally accessible cylinders of radius $r > 0$ and total length L, the rate of increase of canalicular concentration is $\sum_{m=1}^{n-1} k(n,m)X(m,t)/\pi a^2 L$. A fraction of tracer ions move into or out of the canaliculus by diffusion from bone at a rate

$$\frac{\Delta Q}{\Delta t} = D\left\{\frac{\partial^2 Q(r,t)}{\partial r^2} + \frac{1}{r}\frac{\partial Q(r,t)}{\partial r}\right\}\Bigg|_{r=0}. \tag{9}$$

Other ion loss processes such as bone resorption are assumed to occur at a rate $-k(n,n)Q(0,t)$. Thus

$$\frac{\partial Q(0,t)}{\partial t} = \sum_{m=1}^{n-1} \frac{k(n,m)X(m,t)}{\pi a^2 L} + \frac{\Delta Q}{\Delta t} + k(n,n)Q(0,t). \tag{10}$$

Note that we assume no penetration of canalicular territory, i.e., $2\pi rLf(r) = \delta(r)$.

SOLUTION BY INFINITE SERIES

Equations (1), (2), (8), (9), (10) suggest an infinite-series solution based on separation of variables. Greek letters here represent unknown coefficients or constants that depend on the model parameters $a, b, c, D, L, k(i,j)$. The

proposed solutions are

$$Q(r,t) = \sum_{j=1}^{\infty} \alpha(j) U\left(\frac{r\theta(j)}{b}\right) \exp(\lambda(j)t), \tag{11}$$

$$X(i,t) = \sum_{j=1}^{\infty} \beta(i,j) \exp(\lambda(j)t). \tag{12}$$

When (11) is inserted into (2), we have the boundary condition

$$\theta(j)U'(r\theta(j)/b) = -cU(r\lambda(j)/b). \tag{13}$$

For the spatial part of the eigenfunction we assume the same relation that generates $U(X) = J_0(X)$ [hence $U(0) = 1$]:

$$\theta(j)^2 U''(r\theta(j)/b) + \frac{b\theta(j)U'(r\theta(j)/b)}{r} = -\theta(j)^2 U(r\theta(j)/b). \tag{14}$$

This assumption is consistent with (13). When (11), (12) are inserted into (8), for the homogeneous case $A(i,t) = 0$ we obtain

$$\lambda(j)\beta(i,j) = \sum_{m=1}^{n-1} k(i,m)\beta(m,j) + k(i,n)\pi a^2 L\alpha(j). \tag{15}$$

Finally, we insert (11) at $r = 0$ and (12), (14) into (9), (10). Then

$$\lambda(j)\alpha(j) = \sum_{m=1}^{n-1} \frac{k(n,m)\beta(m,j)}{\pi a^2 L} - \frac{D\theta^2(j)\alpha(j)}{b^2} + k(n,n)\alpha(j). \tag{16}$$

Define

$$\beta(n,j) = \pi a^2 L\alpha(j), \tag{17}$$

$$k(n,n,j) = k(n,n) - D\theta(j)^2/b^2, \tag{18}$$

$$k(i,n,j) = k(i,n) \quad \text{for} \quad i < n. \tag{19}$$

Then (15)–(19) yield the infinite algebraic eigensystem

$$\lambda(j)\beta(i,j) = \sum_{m=1}^{n-1} k(i,m)\beta(m,j) + k(i,n,j)\beta(n,j). \tag{20}$$

Note that when $n = 1$, $\lambda(j) = k(1,1) - D\theta(j)^2/b^2$.

The solution of this infinite eigensystem is not very appealing in general; but for lead and other bone-seekers, the time scales $-1/k(i,i)$ for the soft

tissues and blood are all less than 50 days, whereas the diffusion scale b^2/D is on the order of several years, so the tissue and bone kinetics are very separable. On the other hand, for most of the eigenvalue problems of interest to us the sequence $\theta(j)^2$ increases very rapidly, so that the bone-diffusion time scale of several years is quickly reduced to time scales of 50 days or less in the higher-order terms $b^2/D\theta(j)^2$. Thus in many practical problems, it may be possible to truncate the general solutions for small values of j in (11) or (12). We illustrate this in Section 7. It is seen that the main problem is specification of the eigenvalue problem for the bone diffusion, since the calculation of the $\theta(j)$ is primary to the estimation of the rate matrix K when the system eigenvalues $\lambda(j)$ are no longer simply the eigenvalues of K.

BONE-BLOOD-TISSUE MODEL WITH DIFFUSION: COMPARTMENTAL APPROXIMATION

Assume that bone exchanges only with a blood or blood-serum pool in which $i = 1$ denotes the blood compartment. In this case, $k(n,n) = -k(1,n)$. Each value of j determines an eigensystem of size n with diagonal transfer coefficients $k(n,n,j) = -k(1,n) - D\theta^2(j)/b^2$. This suggests that the absorption be partitioned among the various components $j = 1,2,3,\ldots$ corresponding to the eigenvalues $\theta(j)$ of the diffusion equation (5):

(i) Omit compartment n and replace it by "bone components" $n+j$, $j = 1,2,\ldots$.

(ii) Replace the parameter $k(1,n)$ for bone absorption of tracer from blood. Let $k(n+j,1)$ be the absorption into bone component j, where the total rate $k(n,1) = k(n+1,1) + k(n+2,1) + \cdots$ is kept the same.

(iii) Replace the normal loss rate $k(1,n)$ by $k(1,n) + D\theta(j)^2/b^2$ in bone component $i = n+j$. This represents combined loss of tracer from bone due to normal processes such as bone resorption, as well as the return of tracer to blood to slow diffusion to the canalicular boundary at $r = a$. (See Fig. 3.)

The inflow parameters $k(n+j,1)$ into bone component j represent the partition of the total ion inflow in bone into fractions $k(n+j,1)/k(n,1)$ whose typical residence time there is given by $1/[k(1,n) + D\theta(j)^2/b^2]$. There is no direct relationship between such a partition into eigenvalue components and the initial deposition function, which is here taken to be surface deposition at a thin canaliculus.

4. AN ALTERNATIVE APPROACH USING CONCENTRIC RINGS

An alternative data-fitting approach has been described in [1] and was applied to calcium kinetics at bone surfaces in [15]. Instead of representing bone by a single compartment, suppose now that there are $m+1$ bone compartments labeled $i = n, n+1, \ldots, n+m$. Compartment $n+i$ consists of the cylindrical shell from radius $r(i)$ to $r(i+1)$, where $r(0) = a$ and $r(m+1)$

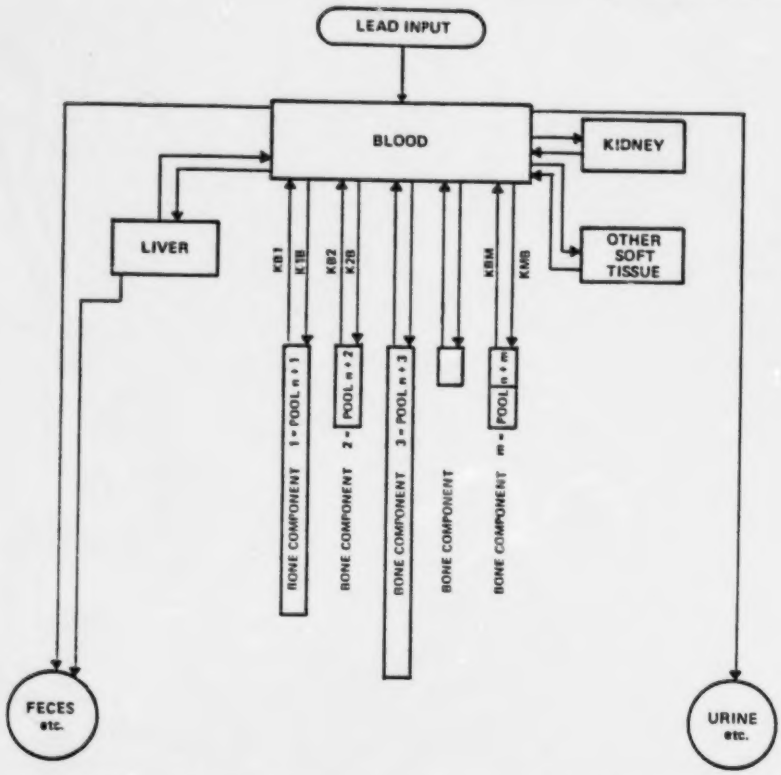

FIG. 3. Mammillary approximation to compartmental model for blood and soft tissues coupled to bone with spatial diffusion. KBM is the fractional transfer coefficient to blood from eigenvalue component m, and KMB is the fractional transfer coefficient from blood to eigenvalue component m.

$= b$, $r(i) < r(i+1)$. The diffusion transfers can be approximated by a linear compartmental model with rate coefficients

$$k(n+i, n+i+1) = \frac{4Dr(i)}{\left[r(i)^2 - r(i-1)^2\right]\left[r(i+1) - r(i-1)\right]} \quad \text{if} \quad i < m,$$

$$k(n+i, n+i-1) = \frac{4Dr(i-1)}{\left[r(i)^2 - r(i-1)^2\right]\left[r(i) - r(i-2)\right]} \quad \text{if} \quad i > 0,$$

$$k(n+i, n+i) = -4D\frac{\dfrac{r(i)}{r(i+1)-r(i-1)} + \dfrac{r(i-1)}{r(i)-r(i-2)}}{r(i)^2 - r(i-1)^2}. \qquad (21)$$

The compartmental boundaries may be specified in advance, so that only the diffusion coefficient D needs to be estimated from the data. The deposition density $f(r)$ may be described by the rate coefficients $k(j,h)$ for $h < n$ and $j > n-1$; the return of the tracer to the soft tissues occurs at rate $k(h,j)$.

The use of a finite number of sequential compartments (catenary model) will introduce a substantial delay in the residence of tracer in the system, but cannot reproduce the long residence times of the diffusion model unless the size of outlying bone compartments is very large indeed. $m = 10$ was used by Groer and Marshall, who showed that the 10-compartment catenary system produced a calculated concentration curve intermediate between that of a 1-compartment model and the diffusion model for a semiinfinite plane solid (as might perhaps have been anticipated). This model may be useable for estimation, provided m is very large (so as to include long delays) and initial deposition occurs only in compartments n and $n+m$, so that the number of rate coefficients that have to be estimated from the data is not too great.

5. APPROXIMATING CYLINDRICAL EIGENVALUES

The computer implementation requires a convenient method for calculating the eigenvalues $\theta(j)$ from the cylindrical diffusion equation. Approximations for small arguments c have been developed by Professor James A. Cochran of Washington State University; these are both necessary for data analysis, and of independent interest. (Copies of the derivation may be obtained from the author.)

We assume here the simplest case, in which the central canalicular channel is of negligible radius $a = 0$, so that (6) is the appropriate equation. Let $\theta J_1(\theta) - cJ_0(\theta) = 0$. The Bessel functions J may be expanded in the complex plane using a modulus-and-phase expansion. Retaining only quadratic terms in asymptotic expansions for small c, one obtains the following approximations. Let $a(0) = 2(2+c)^{0.5}/(4+c)^{0.5}$. Define

$$a(j) = (j-1)\pi + \pi/4. \tag{22}$$

Then, for $j > 1$,

$$\theta(j) = a(j) + \frac{-a(j) - \left(\frac{15}{128} - \frac{1}{8}c\right)/a(j) + \left[a(j)^2 - \frac{63}{64} + \frac{9}{4}c\right]^{0.5}}{\frac{13}{8} + c + \left(\frac{23}{256}c - \frac{135}{2048}\right)/a(j)^2},$$

$$\theta(1) = a(0) \quad \text{approximately.} \tag{23}$$

The approximations (23) are accurate to within 2 percent for $c < 1$ when $j > 1$, to within 1 percent for $j = 1$ when $c < 1$.

If $a > 0$, then the eigenvalues may be found in a similar manner from (2).

6. ESTIMATION USING COMPUTER PACKAGES

In estimating the parameters $k(i, j)$, b^2/D, and c, we can fit the infinite system (12) or (13) in principle, provided there are more observations than parameters. In practice, one would use a standard nonlinear least-squares program such as the SAAM program [16] developed at the National Institutes of Health. Virtually all such programs are limited to a finite number of compartments, a limit which is rapidly approached when one tries to estimate parameters from several soft-tissue compartments as well as the hard-tissue (bone) compartments. In a mammillary or nearly mammillary model such as that developed for lead in Section 7, each peripheral soft-tissue compartment has two unknown parameters (transfer from blood and to blood or central compartment). The eigenvalue-model components all have outflow coefficients of the form $(D/b^2)\theta(j)^2 + k(1, n)$, from (12). Thus, however many components, there are only three parameters D/b^2, c, and $k(1, n)$ that need to be estimated from the data. This is compensated by the need to assume a different inflow parameter for each component, in general. Thus, with some finite number H of bone components $h = 1,2,\ldots,H$, there are $H+3$ bone parameters to be estimated from the data, since the value of c determines the sequence $\theta(h)$. For large H this is much better than estimating $2H$ unknowns. We already suspect that D/b^2 will be very small relative to the other residence-time scales (i.e., there is a very long residence time in bone); thus the use of H components loses little accuracy until j [and thus $\theta(j)$] becomes so large that $\theta(j)^2 D/b^2$ is comparable to the other diagonal terms of the matrix K. With these simplifications, it is seen that we now have an approximate compartmental model in which the bone component is modeled as H peripheral mammillary components, each communicating directly with the central blood compartment, with outflow coefficient $\theta(j)^2 D/b^2 + k(1, n)$. The coefficients from blood to each of the H mammillary bone components may be adjusted to fit the available data.

This approximation is not recommended in general, but only for those problems were $\theta(H)^2 D/b^2 + K(1, n)$ is much smaller than other nonzero outflow parameters. Analytical studies of this approximation would be of interest, but are beyond the author's abilities.

The structure of the eigensystem approximation here is mammillary and is quite different from the physically motivated catenary approximation in Section 4. The catenary approach in Section 4 may also allow extremely heavy-tailed distributions of retention time (i.e. power functions) when the size of the distant concentric compartments is exceedingly large. Because of the wide eigenvalue spacings in this approximation, including the possibility that $\theta(1)$ can be made arbitrarily close to 0 for small values of the parameter c, the approximation proposed here will allow very long retention times in bone. In fact, one could even include a trappy component n with $\theta(0) = 0$.

7. EXAMPLE: LEAD METABOLISM IN BEAGLE DOGS

The method proposed here was applied to data on lead retention in beagle dogs reported by R. D. Lloyd and his associates at the University of Utah [17]. The analysis is reported in detail elsewhere [18] and is briefly summarized here to indicate that the method is feasible. Data were available on lead retention in three beagle dogs (T1L5, T2L5, T3L5) in various compartments and at several times up to 1497 days for T1L5, 28 days for T2L5, and 1100 days for T3L5. The long-term whole-body retention data in T1L5 and T3L5 allowed the possibility of fitting the bone diffusion model. Data on lead retention in liver and kidney were available only for T2L5 at the time of sacrifice, 28 days. However, the three dogs were littermates and had very similar patterns of blood and whole-body lead retention initially, so the liver and kidney retention was assumed to be approximately the same for the other two dogs. The fitted model thus had four soft-tissue compartments (blood, kidney, liver, other tissues), the bone compartment with several diffusion components, and two terminal loss compartments (feces, urine). We assumed the constant lead loss rate from bone was negligible, so $k(1, n) = 0$. The parameters were fitted by the SAAM27 programs assuming an initial

TABLE I

Kinetic Parameters for Compartmental Model with Bone Diffusion in Beagle Dogs[a]

From/to	Parameter ± standard error (day^{-1})	
	Dog T1L5	Dog T3L5
Blood/liver	0.870 ± 0.077	0.750 ± 0.075
Blood/kidney	0.327 ± 0.050	0.266 ± 0.042
Blood/other tissues	0.171 ± 0.032	0.145 ± 0.032
Blood/feces	0.0647 ± 0.0076	0.0635 ± 0.0070
Blood/urine	0.0491 ± 0.0017	0.0424 ± 0.0015
Blood/bone ($h = 1$)	0.0377 ± 0.0057	0.0350 ± 0.0052
Blood/bone ($h = 2$)	0.	0.
Blood/bone ($h = 3$)	0.0662 ± 0.0099	0.0665 ± 0.0100
Blood/bone ($h = 4, 5$)	0.	0.
Liver/blood	0.354 ± 0.036	0.387 ± 0.042
Liver/feces	0.0473 ± 0.0049	0.0410 ± 0.0052
Kidney/blood	2.025 ± 0.253	1.980 ± 0.257
Other tissues/blood	0.244 ± 0.039	0.245 ± 0.045
D/b^2 (diffusion scale)	0.000321 ± 0.000050	0.000290 ± 0.000047
c (gradient coefficient)	0.532 ± 0.083	0.967 ± 0.151

[a]Data from Lloyd et al. [17].

standard-error estimate of 100 percent. All of the estimated parameters in Table 1 showed iterated solutions that were far more precise than this.

The selection of the eigenvalue problem (6) with $a = 0$ was based on estimates of corresponding parameters in humans. Groer and Marshall suggest that the diffusion parameter D for apatite crystals in bone is on the order of $D = 10^{-16}$ cm^2/sec. Marshall [9] also suggests the values $a = 0.085$ microns and $b = 0.75$ microns; thus $b^2/D = 2.29$ years and $a^2/D = 6.5$ days. On the other hand, most of the kinetic parameters for blood-lead and soft-tissue retention in man suggest mean residence times on the order of 20 to 100 days [19]. We would therefore be justified in truncating the approximation when the estimated bone diffusion component had residence times $b^2/D\theta(j)^2$ less than, say, 20 days. This suggests that if lead is quickly dispersed in canalicular territory (as its long residence time in bone suggests), little additional information is lost by ignoring the finite size of the canaliculus. This hypothesis can be explored in more detail when useful eigenvalue approximations for (6) are available.

It is also worth noting in Table 1 that about $\frac{1}{3}$ of the blood lead that went into bone is associated with very long-term retention (mean residence time about 3000 days), and the remaining $\frac{2}{3}$ is associated with component 3 [or $\theta(3)$], which has mean residence time of 60 days. The least-squares estimate of the fraction associated with other components (2, 4, 5) is zero. Perhaps, to a crude first approximation, we may conclude that something like $\frac{2}{3}$ of the lead absorbed into the canalicular territory returns quickly to the original canaliculus and the remaining $\frac{1}{3}$ returns much more slowly.

8. DISCUSSION

The results in Table 1 suggest that both the diffusion parameter D/b^2 and the gradient coefficient c can be estimated from intact animals, as Norwich has shown can be done for spherical diffusion in liver [10]. The approach outlined here should be applicable to any diffusion models for which the eigenvalues can be adequately described by explicit parametric functions of the gradient parameters.

Many authors have derived tracer retention functions in blood $[X(1, t)]$, in bone $[X(n, t)]$, or for the whole body $[R(t) = \Sigma X(i, t)]$, that could be expressed as power functions. For example, the ICRP model can be rewritten as

$$R(t) = A(t + C)^{-B}C^B\left[pe^{-kt} + (1-p)e^{-Lt}\right] + (1-A)e^{-Mt}.$$

In [7] I referred to a large number of papers in which power-function models were derived for tracer retention. Many relevant references were still overlooked, e.g. [21, 22, 23]. In some of these papers, e.g. [22, 23], the argument

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was made that a power-law retention function could be derived as a mixture of a large number of exponentials with a Gamma-type distribution of the rate coefficients. This paper shows that a diffusion model provides one necessary condition for power functions, i.e. an infinite spectrum of exponential coefficients $\lambda(j)$. I have not yet determined that the diffusion model specified in this paper is also sufficient to generate power-law retention functions, since this requires a model for the eigenvalue component partitions $k(n+j,1)/k(n,1)$.

The model developed here does not establish the necessity of fitting all tracer-retention data by sums of exponentials. It does establish a more direct connection between the biophysical model of ion transport by diffusion and the mathematical models for tracer retention involving mixtures of exponentials (in general) or power functions (in particular). The bone-diffusion model is now coupled to the model of well-mixed tissue compartments, and the parameters of the coupled system can be estimated approximately in practice using standard compartmental-analysis programs. Thus the present approach is both more realistic and easier to apply than the semi-Markov model I studied previously [20].

The model developed here also suggests an upper limit to the mean retention time in bone, $b^2/D\theta(1)^2$, which is finite if $c > 0$. Hence the tracer-retention model is not "hermaphroditic" [24], as it would be for purely power-function retention.

The model developed here is computationally more involved than the power-function model. The extra computations may be justified for time-varying exposure patterns in which tissue concentrations for critical organ systems are sensitive to the kinetic mechanisms. This appears to be the case for environmental toxins such as lead [18, 19].

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